CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-465

DRUG PRODUCT: Fluoxetine Capsules USP, 10 mg, 20 mg, and 40 mg.

FIRM: Reddy-Cheminor, Inc.

DOSAGE FORM: Capsules

STRENGTHS: 10 mg, 20 mg, and 40 mg.

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product will be manufactured, processed, controlled, packaged, and labeled at Cheminor Drugs Limited:

Cheminor Drugs Limited
Via IDA Bollaram
Bachepalli- 502 325
India
(OK on 8-1-99).

nufacturer-Active Ingredients:

The manufacturer of the drug substance, Fluoxetine Hydrochloride USP, is:

Dr. Reddy's Laboratories LTD.
Plot No. 137 &138,
Sri Venkateswara Co-operative Industrial Estate,
Bollaram, Narsapur Tq.
Medak Dt.
Andhra Pradesh, INDIA
DMF
(OK on 8-1-99).

Contract Laboratories:

None except analysis of container/closure system

This outside Laboratory will perform the container testing for the container/closure systems.

2. Dr. Reddy's Research Foundation

Bollaram Road, Miyapur
Hyderabad 500138
Andhra Pradesh, India

This outside Laboratory performed the Differential Scanning Colorimetry (Thermal Analysis) testing for the container/closure systems.

BIO STUDY:

Satisfactory per K Dhariwal reviewed on 11-8-2000 for 10 mg, 20 mg and 40 mg.

10 mg strength: in vitro dissolution testing
I. Executed batch #001A, USA
II. Executed batch #001B, Canada

20 mg strength: Bio-batch study and fasting and non-fasting conditions
I. Executed batch #001[Lot I], USA
II. Executed batch #001[Lot II], Canada

40 mg strength: in vitro dissolution testing under fasting
Executed batch ##E001

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Compendial drug substance and drug product.
This product is now the subject of a USP monograph so no FDA sample testing is required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration dating:

2 years expiration date with 1, 2 and 3 month accelerated stability data (40°C/75% R.H.) and 3 month room temperature stability data (25°C±2°C/60%±5%) on batch No.:001A for 30's and 100's (85 cc HDPE bottle) capsules package sizes for 10 mg, and on batch No.:001 (Lot-1) for 30's, 100's (85 cc HDPE bottle) and 1000's (950 cc) capsules package sizes for 20 mg, and on batch No.:E001 for 30's, 500's and unit dose blister (10's - only 3 months accelerated) capsules package sizes for 40 mg.

LABELING:

Satisfactory per A. Vezza reviewed on 6-8-2001 for TA letter only.

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

10 mg strength:
I. capsules (executed batch #001A, USA)
II. capsules (executed batch #001B, Canada)

20 mg strength:
I. capsules (executed batch #001[Lot I], USA)
II. capsules (executed batch #001[Lot II], Canada)

40 mg strength:
capsules (executed batch ##E001)

DMF was reviewed and found satisfactory by L. Tang on 2-24-2000.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

10 mg strength batch # batch #001A: cap batch size

20 mg strength batch #batch #001[Lot I](Bio-batch for fasting and non-fasting conditions): cap batch size

40 mg strength batch # ##E001 (in-vitro for fasting conditions):
cap batch size

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

10 mg strength capsules

20 mg strength Capsules

40 mg strength capsules

The proposed production batches have the same manufacturing process as the test batches or Bio-batches (see above). Scale-up meets OGD PPG 22-90.

CHEMIST: Lucia C. Tang DATE: 6-12-01

SUPERVISOR: Ubrani Venkataram DATE: 6-14-01

/S/ 6/20/2001.

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1. CHEMIST'S REVIEW NO. 6

2. ANDA # 75-465

3. NAME AND ADDRESS OF APPLICANT

Reddy-Cheminor, Inc.
U.S. Agent for Cheminor Drugs Ltd.
66 South Maple Avenue
Ridgewood, NJ 07450

4. LEGAL BASIS FOR ANDA SUBMISSION

Innovator Drug: Prozac
Innovator Company: EliLily
Patent Expiration Date: 11-11-99.
Two Patents are still in effect for the innovator:

4,626,549 has two use codes and expires 12-2-03- but this patent has gotten pediatric exclusivity and now expires 6-2-04.

4,234,081 is for the chemical entity itself and expires 2-2-01- this patent also got pediatric exclusivity and now expires 8-2-01.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Fluoxetine Hydrochloride Capsules, 10 mg, 20 mg and 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

9-24-98: Original submission
9-14-99 Amendment for 1st NA letter
9-20-99: Amendment for additional strength (40 mg)
11-18-99: Patent amendment
12-10-99: Amendment
5-9-2000: Amendment

12-26-2000: Amendment
3-8-2001: Amendment
3-30-2001: Telephone Amendment
5-25-01: Labeling amendment
7-19-01: Labeling amendment
7-30-01 and 7-18-01 : Amendments
FDA: HV 8/1/01.

11-19-98: Acknowledgment
6-15-99: 1st NA letter for 10 mg and 20 mg
3-20-2000: 2nd NA letter for 10 mg, 20 mg and 40 mg
11-16-2000: 3rd NA letter for 10 mg, 20 mg and 40 mg
3-08-2001: 4th NA letter
3-16-2001: Letter concerning labeling
3-29-2001: Telephone request

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF

13. DOSAGE FORM

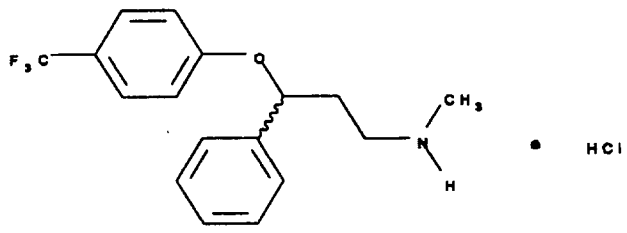
Capsule

14. POTENCY

10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Fluoxetine Hydrochloride
Formula: $C_{17}H_{18}F_3NO.HCl$; Molecular weight: 345.79



(±)-*N*-Methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-toly)oxy]propylamine monohydrochloride. CAS [59333-67-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

July 18, 2001 Labeling amendment was reviewed and found acceptable per A. Vezza on 7-x-2001.

Status:

a. EER status: Acceptable

EER was requested for Cheminor and Doctor Reddys Laboratories by Tim Ames on December 3, 1998 and found acceptable August 1, 1999.

b. Method Validation status: Adequate

Not required since both drug substance and finished product are official USP items.

c. Bio-review status: Satisfactory for 10 mg and 20 mg

Satisfactory per K Dhariwal reviewed on 12-8-98 for 10 mg and 20 mg.

d. Bio-review status: Satisfactory for 40 mg

Satisfactory per K Dhariwal reviewed on 11-8-2000.

e. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 7-30-2001.

f. DMF : Satisfactory

DMF has been reviewed and found satisfactory by L. Tang on 4-12-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval, 10 mg and 20 mg for 2nd TA, 40 mg for full Approval.

19. REVIEWER: Lucia C. Tang

DATE COMPLETED: 7-28-2001

Redacted 23

pages of trade

secret and/or

confidential

commercial

information

Chem #6

JUN 15 1999

38. Chemistry Comments to be Provided to the Applicant

~~AADA~~/ANDA: 75-465 APPLICANT: Cheminor Drugs Limited

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 mg and 20 mg

The deficiencies presented below represent Major deficiencies.

A. Chemistry Deficiencies

1. Regarding components and composition:

   a. We note that Ferric Oxide black are present in the formulation of the 10 mg and 20 mg. Please provide the amount of iron oxide per capsule for the 10 mg and 20 mg capsule. This is required in order to comply with 21 CFR 1200 which limits the amount of elemental iron to not more than 5 mg per day.

   b. Please include the empty capsule weight for each strength in the composition statement.

   c. Submit the revised composition of the drug product based on the above comments.

2. Regarding gelatin capsules:

   Submit the tests and specifications for imprinting inks. Also, provide information along with certification that the ink meets all the requirements of the indirect food additives regulation 21 CFR parts 174-178, 181 and 182.

3. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

   a. Please provide the control limit of empty capsule weight variation, weight variation of filled capsule and content for each strength (pages 3311-3326 for 10 mg and pages 3389 - 3404 for 20 mg) in the blank batch records.

b. We note that in-process specifications for blend uniformity were provided as % with relative standard deviation not more than % (pages 3605 & 3634 of the original submission). However, we recommend blend uniformity analysis acceptance criteria as % (mean of individual test results) with a relative standard deviation (RSD) of NMT %.

c. Blend homogeneity testing should be specified for the production batches.

4. We note that 85 cc HDPE and 950 cc HDPE bottles were used for packaging 30's, 100's and 1000's package size for Fluoxetine Capsules, 10 mg and 20 mg. However, 60 cc, HDPE bottle, 100 cc HDPE, 200 cc HDPE, 300 cc HDPE, 500 cc HDPE, 750 cc HDPE bottles were provided in (Pages 3770-3782) for container diagrams. Please clarify use of those containers.

5. Submit the actual torque test for cap removal covering the 30's, 100's and 1000's capsules package sizes for each strength.

6. Regarding finished product:

a. USP 23 Supplement 7 and COA of your finished product indicates that "not more than % of any individual impurity is found, and not more than % of total impurities is found" of drug product Chromatographic Purity. Please revise your related substances specifications in in-process testing in capsule filling stage to be consistent with current compendial requirements and your own finished product specifications and resubmit the COA in the capsule filling stage (see pages 2624, 4228, 4233, and etc.)

b. Please provide complete description of drug product in the finished dosage form (pages 4228 & 4231) to be consistent with those in the stability protocol (pages 4285 & 4286).

c. Please include brittleness tests in the finished dosage form and stability studies.

7. Your application fails to contain a satisfactory stability protocol and supporting stability data. In this regard:

a. Please include composition of the drug product in stability report.

b. Please include brittleness tests in the stability studies.

c. We note that the descriptions of the drug product in the stability protocol (pages 4285-4286) is different from those in the stability data report (4292-4313). Please be consistent.

d. On page 4291 you have explained your reason for not including moisture test and specification in the stability protocol. However, it is included in the stability data report. Capsules products are more susceptible to moisture. We strongly recommend that you include a test and specification for moisture in the stability protocol. Please revise and resubmit.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You are advised that microbiological testing should be conducted on each lot of components, prior to use in the manufacture of the drug product, for those components for which the microbial limits test is specified by USP/NF [21 CFR 211.84 (d) (6)]. A 12-month retest period is recommended.

2. DMF has been reviewed and found deficient. A letter outlining the deficiencies has been sent to This ANDA cannot be approved until these deficiencies have been resolved.

Sincerely yours,

/S/

Florence S. Fang
for Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 8 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-465 APPLICANT: Cheminor Drugs Limited

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 mg, 20 mg and 40 mg

The deficiency below represents a Fax deficiency.

The chemistry review is acceptable at this time.

Please submit labeling as directed by the Labeling Review Branch in the Fax to you dated January 12, 2001. Please do not respond to this deficiency letter until your labeling has been found to be satisfactory by the Labeling Review Branch.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research